INFECTIOUS ARTHRITIS: A BACTERIOLOGICAL CONTRIBUTION TO THE DIFFERENTIATION OF THE "RHEUMATIC" AFFECTIONS.

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I. Introduction.

It is surprising, considering the frequency with which "rheumatic" joints of unknown origin, and not referable to commonly accepted types, are met with in any general hospital or similar private practice, that so little is known of the actual etiology in this large group of cases.

The report here presented deals particularly with three cases of this nature in which the bacteriological findings have appeared of sufficient importance to warrant consideration in detail. The fourth case is one of typical acute articular rheumatism. In order to show their relationship, clinically and otherwise, with rheumatic disturbances in general, I wish to refer briefly to that classification of rheumatic joint affections which seems best to accord with our present knowledge.

CLASSIFICATION OF RHEUMATIC AFFECTIONS.

Exclusive of simple traumatic cases and of suppurative conditions of pyogenic or mixed bacterial origin, the term *rheumatic affections* is here used broadly to include cases in which joint symptoms form a more or less prominent feature.

1. Tuberculous and secondary syphilitic joints find a place here, as do also certain arthritides in which a specific bacterial cause has been determined—gonorrhœal, pneumococcic,* etc. Here, too, though with less certainty as to their exact nature, we may include joint involvements directly following specific infections elsewhere in the body[1] [2]—typhoid fever, scarlet fever, measles, dysentery (Shiga's), influenza.

2. As examples of arthropathies of nervous origin may be cited those of tabes, syringomyelia, neurasthenia, and of certain cases of peripheral neuritis.

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* The majority of pneumococcic joints, however, proceed to suppuration. Cave, in Lancet, January 12, 1901, has reported thirty-one cases collected from the literature up to that time, nearly all suppurative.

3. The articular disturbance following administrations of diphtheria antitoxin illustrates cases of toxic origin.

4. Another class of cases may be attributed to hereditary and diathetic conditions—*e. g.*, those seen occasionally in hæmophilia. Gouty joints, both the acute and the so-called chronic types, have been variously classed as toxic or as diathetic.

This would account for practically all the sharply acute inflammatory conditions except those we are accustomed to designate as the acute articular rheumatism occurring in rheumatic fever. Reference will be made later to the claims of this condition to classification with the infectious arthritides.

5. Beside these there yet remain several other conditions which have been reserved to the last because of the great confusion and disagreement that has followed attempts to differentiate them; for this reason Osler and others have preferred to consider them collectively under the name of *arthritis deformans*. In this group it is probable, in the light of recent work, that we have to differentiate at least two distinct classes of cases—those in which *changes of an essential nature occur in the bones and cartilages* of the joints involved, and those in which *such changes are absent or are secondary* to the primary lesion. It seems possible that these two classes are also etiologically distinct, and that the latter are of infectious origin.

It is to this latter class that my first three cases belong. In referring to it I shall use the name first applied to it by Schüller[3]—*infectious "polyarthritis chronica villosa."* It will be more profitable to examine at once the character of these cases themselves before discussing the propriety of grouping them with others under the head of *arthritis deformans*.

INFECTIOUS POLYARTHRITIS CHRONICA VILLOSA.

Clinical Characteristics. This is an affection which may develop at any age, in infancy or in adult life. Marantic conditions predispose to and often definitely introduce it. It follows sometimes upon parturition. A varying degree of constitutional disturbance may mark the onset, though this is often entirely absent and the first symptoms may appear in the joint without any assignable cause. With little or no warning a joint may become sensitive and quickly exhibit signs of an acute inflammatory nature. The local picture at the onset is so similar to that in rheumatic fever that it needs no description. As in the latter condition, several joints are generally attacked in rapid succession, as a rule the larger articulations, though the small joints of the hand are frequently involved as well. The local symptoms are usually milder, but may approach in severity those of rheumatic fever. Some enlargement of the neighboring glands is not uncommon. A moderate leukocytosis is the rule in the early stage; the pulse rate is almost invariably high

(95 to 110) in adults, but there is generally little or no pyrexia. The heart is rarely affected; chorea and subcutaneous nodules* have not been noted.

So far there is little to distinguish these cases from mild forms of rheumatic fever; their *subsequent course*, however, is very different.

In the latter condition the course throughout is essentially acute, the *restitutio ad integrum* of the joints being rapid and characteristic. Directly the opposite is true of the class of cases in question. With frequently no interference with the general health the course is protracted, and the acutely inflamed joints of the early stage acquire a chronically congested and much hypertrophied synovial membrane which permanently deforms the joint. Recurrences of the acute condition after intervals of comparative quiescence are characteristic. From continued disuse shrinkage of the capsule may occur, and contractures of the surrounding muscles, eventually, though rarely, leading to true bony ankylosis, but the entire absence of essential lesions of the bone or cartilage sharply distinguishes it from the *atrophic* or *hypertrophic arthritis* of Goldthwait.[2] Chronic hydrops may continue to be a feature for a longer or shorter period; it is of the character of a transudate, never, apparently, exudative. When the process has not been unusually protracted so that contractures have occurred, the only interference with function is that presented by the hypertrophied synovial folds which act as foreign bodies in the joint. As in other conditions in which such villi are developed it frequently happens, however, that these become adherent to various portions of the synovial walls, and unless proper attention be given to breaking up such adhesions a permanent disability may result.

Pathological Characteristics. The examination of such joints after characteristic changes have developed shows a condition of villous hypertrophy of the synovial membrane. The character of the tissue varies considerably with the stage of the disease—in the recent cases frequently showing marked turgidity and congestion, later often acquiring a comparatively anæmic character. The histological picture varies accordingly. The occurrence of obliterating endarteritic changes may cause necrosis, with rupture of the pedicle and production of joint-mice. Occasionally a general synovial thickening takes place and definite villi are absent. After sufficient quiescence lipomatous transformation of villi is not uncommon; metaplasia into bone or cartilage is observed fairly frequently, and at other times deposits of amorphous lime salts. The fibrous capsule is generally thickened.

Very similar changes are produced in a variety of other conditions, due to local inflammations from various causes. Interesting as these are, their consideration here is not to the point. Painter and Erving[4] have discussed the subject at some length, and with numerous references to the work of others. Schüller,[5] in 1900, in the course of a series of communications, described the histological differences in the synovial villi produced in various conditions, illustrating with cuts.

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* Though mentioned by Bannatyne (Rheumatoid Arthritis, 1898, p. 74) it is uncertain as to what class of cases he there refers.

Compared with the *histological* picture presented by these other villi of various origins, it may be said of those arising in *infectious polyarthritis chronica villosa* that they differ from the former in showing a more extensive thickening of the synovial membrane and a tissue of more cellular character. Moreover, the character of the cells themselves differs with some constancy, for in addition to the large fixed cells with large, clear, vesicular nuclei which, together with their supporting framework of branching fibrous trabeculæ, form the structural background in almost all villi, we see here numerous plasma cells, and a disproportionate increase of infiltrating small round cells, and, in cases where the process is still active, great numbers often of polymorphonuclear leukocytes and eosinophiles. The lymphoid cells appear particularly as a continuous zone beneath the free surface, but nodular aggregations of considerable size are often met with in the deeper layers, especially about the numerous bloodvessels. The lymph channels are large and abundant. The free endothelial border of the synovial membrane often shows several layers of cells instead of the normal, single, flat layer.*

The histological picture is always beautiful. Though moderately characteristic in certain stages, it can never, of course, be relied on as in any way of diagnostic value. The gross anatomical picture is of more value, but it is the clinical features that are of chief importance. As to the value of the x-ray picture in the differential diagnosis from *atrophic arthritis* Goldthwait[3] speaks positively.

It is not my purpose to describe these cases further than will suffice to illustrate clearly the class with which we have to deal. It must be added that clinically they may display very considerable variation from the general type outlined above, *all characterized, however, by a course of a chronically infectious nature, polyarticular, with the production of permanent changes in the joints, affecting primarily only the periarticular structures, and having little or no tendency to display lesions elsewhere in the body.*

Relation to Arthritis Deformans. Nomenclature. It is necessary for the sake of clearness to touch briefly on this subject. Of the many terms applied to certain chronic deforming diseases of the joints, the most commonly used in this country is *arthritis deformans*, and it is just as well to disregard the numerous other terms synonymously employed.

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* In one case (synovial villi removed from the wrist-joint in a case that had presented typical clinical and pathological features) the cells of the free border had acquired a cuboidal form.

Osler's classification is probably the best known. His subdivisions under this head are: (1) Cases with Heberden's nodes; (2) general progressive arthritis—polyarticular, and occurring both as acute and chronic forms; (3) monarticular forms; (4) vertebral —spondylitis deformans; (5) Still's disease.

Goldthwait, on the other hand, makes but three subdivisions, based rather on the pathology and supposed etiology. These are: (1) Hypertrophic arthritis*—including Osler's subdivisions (1), (3) and (4), characterized by essential hypertrophic changes in the bone, supposedly due to disordered metabolic conditions. (2) Atrophic arthritis, including cases of similar nature, characterized, however, by primary atrophy instead of hypertrophy, the changes first appearing in the articular cartilage and thence extending to the bone—it is evident that only part of Osler's subdivision (2) belongs here. (3) Infectious type, including the remainder of Osler's subdivision (2), together with all cases of Still's disease. The latter are included here in the belief that they are merely manifestations in childhood of the same conditions, Still having described only the most striking —*i. e.*, the fatal cases.

This last subdivision of Goldthwait's is identical with the class of cases I have called *infectious polyarthritis chronica villosa.* As these cases differ clinically, pathologically, and probably etiologically† from the hypertrophic and atrophic types there appears good reason to restrict the application of the term *arthritis deformans* to the latter two forms, which have important features in common. Goldthwait retained the "infectious type" under the general head, apparently as a concession to our usually accepted classification, to avoid confusion, and for lack of definite proof as to their etiology. Of more significance is his mention of this same class of cases in his article[2] entitled "Infectious Arthritis" (pp. 6 and 8).

Henceforth in speaking of *arthritis deformans* I shall have reference only to the cases of the hypertrophic and atrophic types.

The name of Max Schüller, of Berlin, deserves mention with this group of cases, for his is the honor of being the first to distinguish them as such. This he did first in a paper[8] presented to the XXI. Cong. der Deutsch. Gesellschaft f. Chir. in 1892.

Again,[3] in 1897, he differentiated them clearly from cases of *arthritis deformans* by the absence of essential changes in the articular structures proper, but was unwilling to commit himself as to their exact relation to ordinary acute articular rheumatism. His report was based on the observation of 56 cases. The condition he termed "*polyarthritis chronica villosa,*" and distinguished two types: (1) with chronic capsular thickening and great synovial hyperplasia, resulting in a greatly deformed joint with marked limitation of motion and persistent pain; (2) with capsular atrophy and villous formation limited to only a small area, pain a feature as above. As to his bacteriological findings I shall have occasion to speak later on. His descriptions are brief and clear, and are worthy of examination.

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* In his earlier writings Goldthwait distinguishes *osteoarthritis* and *rheumatoid arthritis.* These terms are synonymous with *hypertrophic* and *atrophic arthritis*, which were subsequently adopted as being more accurate and less confusing.

† McCrae (Journal of the American Medical Association, October 8, 1904) states his belief that all three forms are of infectious origin, but there is no scientific evidence in support of this. As to the work of Bannatyne, which is supposed to favor this view, reference is made later.

Subsequent observers, especially in England,* and certain writers in this country have referred to Schüller's work, but have failed to recognize the truth of his distinctions, and have confused his cases and their own with forms of true arthritis deformans. Thus, in reviewing the literature with reference to the special group of cases in question, it is always necessary to take into account the clinical and pathological features of the reported cases, and to disregard the various terms according to which their observers have classified them.

Speaking of the same group of cases distinguished by Schüller, Goldthwait[3] writes: "It is also possible, and indeed probable, in the light of recent reports, that organisms have been found, or will be found, which will explain some of the cases which, up to the present time, have been shown to be undoubtedly infectious, but in which the definite organism could not be found." These words may well serve as an introduction to the following report:

II. REPORT OF CASES.

In the collection and disposition of the materials used for bacteriological purposes particular attention was paid to avoiding contaminations.

CHANCES OF ERROR. TECHNIQUE.

This is mainly a consideration of the opportunities and possibilities of contamination. Where *aspiration* is employed there are three special sources of danger.

(*a*) Contamination from the *skin*. It must be conceded that this is possible, though reduced to a minimum by suitable preparation of the patient. In all my cases the parts were prepared as for a major operation, in most of them a bichloride poultice was worn for the preceding twenty-four hours. The organisms cultivated are not such as we recognize as the ordinary inhabitants of the skin.

(*b*) Contamination from the *air*. It is but fair to draw attention to this ever-present source of error. All manipulations were planned with reference to avoiding this. The syringe, after sterilization, remained covered until required; it was handled with properly disinfected hands, and care was taken not to touch the needle itself. Inoculation of tubes was made at the bedside, plugs and mouths of tubes well flamed, and transfers carried out as rapidly as possible.

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* The recent references by W. Hale White, and by A. E. Garrod to this group of cases are, however, definite. Lancet, March 18, 1905.

(c) Contamination from the *syringe*. This was avoided by using an instrument all parts of which could be boiled, being entirely of glass with the plunger wrapped with asbestos, and with a stiff rubber connection for the needle. These were boiled for fifteen minutes before using, and resterilized before aspirating a second joint of the same patient.

Cases in which material was obtained at *operation*. Contamination from the *air*. This is practically the only source of error here. My practice has been to have on the table, covered in the bag in which they were boiled, a graduated glass of suitable size and a small glass funnel. Before opening the capsule, and after bleeding is well controlled, the glass is taken from the bag and held close to the capsule, the wound being well retracted. The capsule is then nicked and contents allowed to escape into the glass.* The latter is at once covered with a fresh sterile towel that has not been exposed to the air, and as soon as possible the contents are rapidly transferred to a sterilized, cotton-plugged flask, the small funnel being used for this. If sufficient fluid is not obtained cultures are made directly from the joint on blood-serum tubes, and smears are likewise prepared. Any bits of tissue removed from the joint are at once folded between sterile sponges that have not been exposed to the air.

Notwithstanding all these precautions there remains, theoretically, a considerable chance for contamination. That this will seldom occur is shown: first, by the larger number of cases in which no organism was cultivated; secondly, by the consistent results obtained in the other cases where the same organism grew in pure culture in tubes inoculated from different joints of the same patient, or in tubes inoculated separately with the fluid, and with the tissue from the same joint. In the case of rabbits, where chance of contamination is much greater, it is worthy of note that out of thirty-nine aspirations from which cultures were attempted, all either remained sterile or yielded in pure culture the organism injected, excepting two tubes which were contaminated.

From 9 cases of various clinical types cultures from the joints were attempted on blood serum. Of these only 4 gave positive results. The negative cases were as follows:

Negative Cases.

No. 5. Mr. M. (Corey Hill Hospital, Dr. Goldthwait.) *Atrophic arthritis* (many joints). All cultures remained sterile. They were taken from the knee-joint fluid obtained by aspiration, and later at operation, and numerous tubes were inoculated. The attempt was also made to grow cultures in large quantities of bouillon after Blaxall's* method. Three blood-serum tubes were also inoculated with bits of snipped-up synovial tissue from a small quantity removed at operation. No organisms were seen in smears fromthe fluid.

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* Dr. Leary has suggested a much simpler and safer method—viz., the aspiration of the fluid through the capsule after the skin incision is made.

No. 6. Miss H. (Carney Hospital, Dr. Painter.) Considered to be an early *atrophic arthritis*. An afebrile polyarthritis with acute pain and slight effusion in left knee-joint. At time of aspiration the effusion had practically disappeared, but a few drops of clear fluid were withdrawn from the left knee-joint and two plain blood-serum tubes and one blood-smeared tube inoculated. The two plain tubes remained sterile, the third tube was doubtless contaminated. Smears from needle-point negative.

The culture medium in the third tube was blood serum that had been smeared with placental blood (collected aseptically and kept on ice in Ehrlenmeyer flasks). A number of such tubes were prepared and incubated for several days before use, but as many which were not used, but remained in the incubator, developed growths after a longer period (seven to ten days), no cases are reported as positive in which this medium was used.

No. 7. John W. (Carney Hospital, Dr. Painter.) *Infectious arthritis following influenza.* This was a comparatively recent elbow in which, however, synovial fringes had developed and proliferation had been stimulated in the head of the radius. Cultures were made from the synovial fluid, which, though thick and syrupy, was clear and but slightly in excess. Bits of synovial tissue, and bone removed from head of radius were also placed in separate tubes of the blood-smeared serum. No growths were obtained save such as were clearly contaminating. Smears from synovial fluid negative.

No. 8. Arthur L. (Carney Hospital, Dr. Minot.) *Acute articular rheumatism.* This was a first attack, in both wrists and knees and in one elbow, with mitral insufficiency. The arthritis subsided quickly and at time of aspiration only a drop or two was obtained from either knee-joint. Blood-serum tubes inoculated, but remained sterile; smears from needle-point negative.

No. 9. Miss A. (N. E. Baptist Hospital, Dr. Goldthwait.) *Chronic infectious arthritis* (many joints). This represents the border-line cases, in which, though of evident infectious origin, and without essential bone or cartilage involvement, permanent peri-articular change has been produced, without, however, well-marked villous proliferation. It seems likely that subsequent attacks might produce the typical picture described by Schüller.

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* Lancet, April 25, 1896. It was realized, however, that the cases with which Blaxall worked, though described as "rheumatoid arthritis," were undoubtedly not of the atrophic type, but of the variety differentiated by Schüller.

The left knee-joint was aspirated under cocaine anæsthesia, with rigid aseptic precautions, and three or four drops of fluid obtained. Two tubes were inoculated, one of plain and one of blood-smeared blood serum. Smears from needle-point negative. Two days later a pure culture was discovered on the plain tube—a motile, pale-staining bacillus, decolorized by Gram's. The organism grew in discrete, round, elevated, colorless colonies, not visible to the naked eye until the third day; when fused, indistinct granular patches appeared. It was very difficult to obtain smears, apparently from unusual coherence of the organisms, and the firm, membranous-like character of the colonies, so that it was necessary to pick a colony up bodily and crush it on the slide; even then few isolated organisms were found compared with those that remained *en masse*. Subcultures on fresh blood serum developed slowly, the colonies later acquiring a yellowish hue.

On the second day after aspiration the blood-smeared tube also showed a growth similar in character to that described, but because of inability to obtain the organism in smears the colonies were regarded as perhaps oil-droplets or something else extraneous, unlikely as this appeared. A subculture on fresh serum was attempted, however, and yielded a pure culture from which smears were successfully made, showing presence of the same organism above described from the original—not the parent—tube. This organism was not of the character of the contaminating cocci that grew on many of the blood-smeared tubes. Moreover, it was found in pure culture on *both* the original tubes, one of which contained plain blood-serum. Nevertheless it is thought unfair to include it with the report of positive cases, although of sufficient interest to warrant consideration because of its similarity in certain respects to the spore-bearing organisms isolated in three of the positive cases. Besides it bears, so far as studied, a considerable resemblance to Schüller's and Blaxall's bacilli. It is hoped that another opportunity may be offered to study this case.

Positive Cases.

CASE I.—Frank A. L., Massachusetts; aged twenty-eight years; machinist. Admitted April 27, 1904. Carney Hospital, orthopedic service, Dr. Painter.

Complaint. Stiffness of various joints; persistent swelling in knees.

Family History. No tuberculosis, neoplasm, or joint affections.

Personal History. Gonorrhœa at age of eighteen; no complications. Measles at age of twenty-four. No history of chronic diseases (except of joints), chorea, or any nervous disorders. General health always good. No history of traumata or surgical operations.

Joint History. At age of seventeen, eleven years ago, developed moderate pain, with stiffness, in both hips; onset sudden, preceded by chill, following exposure to cold and wet; not in bed, but off feet for two to three weeks; no subsequent attack in hips. For past four years has noted moderate tenderness about shoulders, with some stiffness in those joints. One year ago, April, 1903, having gone to bed in excellent health, woke with severe dull ache in both knees; considerable swelling, but no redness or heat. Condition continued unchanged for four months, not preventing work; since then knees have remained swollen, but painless, excepting on attempting to use joints after some inactivity. Eight months ago noted stiffness, without pain, developing in neck. Appetite good; sleeps well; bowels regular.

Physical Examination. Poorly developed, emaciated, pale. *Chest* symmetrical; expansion (across nipples) limited to 1.5 cm. *Lungs* negative. *Heart* of normal size and position; both sounds clear; at the apex a soft systolic murmur, faintly transmitted to the axilla, not heard in back. *Abdomen* negative, spleen and liver not felt. *Glands:* moderate, soft enlargement of posterior cervical, right axillary, and both inguinal groups. *Reflexes:* knee jerks present and equal; ankle clonus fairly distinct on left; no Babinski.

Special Examination. Spine: Stands with considerable list to the right; back shows a long, gentle kyphotic curve, of postural variety, with a double scoliotic curve, and no apparent rotation; cervical spine slightly flexed forward; practically no motion whatever permitted by spine, except to a slight degree in cervical region. *Shoulders:* rotation free; all other motions much restricted. *Elbows, wrists, hands,* negative. *Hips:* habitual slight flexion and abduction hips very stiff, but with some manipulation, flexion, abduction, and adduction can be carried to almost normal limits; rotation about one-half normal; symmetrical atrophy of both thighs. *Knees:* both are symmetrically enlarged throughout the synovial outlines of the joint; no redness or heat; not sensitive to palpation; patellæ freely movable and do not float; swelling feels boggy and soft, irregular masses can be felt to glide under the examining fingers; no bony thickening made out; both knees can be completely extended; flexion beyond 135° in right and 100° in left, is painful and resisted by patient. *Feet* and *ankles,* negative. *Temperature,* 101°. *Urine,* negative. *Blood:* not examined.

Operation, April 29, 1904; Dr. Painter. Incisions made on both sides of patella of left knee about 10 cm. in length. The fibrous capsule was somewhat thickened, the synovial capsule much thickened and very villous. The villi were quite vascular, and in greatest abundance about the border of the patella and along the edge of the femoral condyles. There was no excess of fluid in the joint, but a blood-serum tube was inoculated with a loopful. The cartilage was clear and glistening, and not eroded. The ligamentum mucosum was considerably thickened. The villi here and about the condyles and patella were trimmed out and the capsule closed with interrupted silk. Skin closed with continuous subcutaneous silkworm gut. A voluminous dry dressing was applied to the extended knee.

The skin sutures were removed at the end of one week, and moderate passive and active motion begun. On the twelfth day functional use was permitted. Operation on the other knee refused by patient.

May 14, 1904. Has been walking about for past two days with no pain or apparent weakness. General condition excellent. Discharged, with flannel bandage about knee, to report in one week.

The highest temperature was on admission, 101°, varying thereafter from normal to 99°.

Nothing has been heard from the patient since last note, and attempts to locate him have failed.

Bacteriological Report. A loopful of serum, obtained from the left knee-joint at operation, was inoculated into a tube of plain blood serum. Upon this, in pure culture, developed an organism whose morphological and cultural characteristics are described later in the outline. This tube was put on ice, and for lack of opportunity was not studied until five months later. It was feared the culture had died out through drying down of the medium, but being a spore-bearer it was readily revived in pure culture, and showed the same characteristics as before. Its identity is further established by the finding in the tissue removed at operation of an organism of the same morphology and staining (Gram's) properties, as well as by the results of animal experimentation.

The synovial tissue removed at operation was hardened in 80 per cent. alcohol for histological examination. It consisted of a large handful of coarse, thickly-set villi, not very vascular. Sections stained by the Gram-Weigert method showed the presence of the bacillus in small numbers, lying mainly in the lymph channels or cells at some distance from the free border. The character of the tissue corresponds histologically with the description in the introductory section. The animal experiments are described under a later heading.

Case II.—Aaron B. R., Nova Scotia; aged thirty-eight years; marine engineer. Admitted January 5, 1905. Carney Hospital, orthopedic service, Dr. Painter.

Complaint. Pain and swelling of right knee.

Family History. Negative; no joint affections.

Personal History. Has had various diseases of childhood. Gonorrhœa three times, the last fifteen years ago. No history of chronic diseases, nor of any previous joint troubles.

Present Illness. Seven months ago began to have sharp pains in right knee, radiating up the thigh, aggravated by frequent kneeling at work. One month ago joint was subjected to a sudden strain; since then pain has been continuous, and joint swollen except for brief periods of enforced rest. Kept at work until a few weeks ago.

Physical Examination. Well developed and nourished, color good. Lungs, heart, and abdomen negative. Condition of glands not recorded. All joints negative except right knee. *Right knee:* Capsule much distended and patella floats. Thickened irregular masses can be felt, apparently within the capsule. Motions of joint considerably restricted. Circumference across patella 5.5 cm. greater than on left side; 3 cm. atrophy of right thigh and calf. *Temperature* normal. *Urine* negative. *Blood,* hæmoglobin, 80 per cent.; red blood corpuscles, 6,000,000; white blood corpuscles, 12,600.

Operation. January 10, 1905. Dr. Painter: Incision made on inner side of patella of right knee, about 8 cm. in length. Before opening the capsule all bleeding was controlled and wound well retracted. Through a small incision in the capsule about three ounces of serous fluid was allowed to escape into a sterile flask. Capsular incision was then extended. Bone and cartilage were normal. The whole synovial membrane was thickened and rough. Villous masses depended from the internal alar ligament, and a pannus-like fold of synovial membrane overlay the inner surface of the internal condyle. These tissues were removed, and operation completed as described in Case I., the after-treatment being carried out in same manner.

January 24th. Discharged, wearing flannel bandage over knee. Temperature practically normal throughout stay in hospital.

Bacteriological Report. 1. *Serum.* About ℥iij were obtained, rather syrupy and cloudy but not flakey, of light urinous color. 2 or 3 c.c. were removed with a sterile pipette, transferred to a tube of plain blood serum, and incubated at 37° C. No growth ever appeared on this tube, which was discarded after two weeks.

Two centrifuge tubes, which had previously been plugged with cotton and sterilized one and a half hours by dry heat at 150° C., were half-filled with serum removed with the sterile pipette, and contents centrifugalized for three minutes. From the bottom of one of these tubes two or three drops were removed with a freshly sterilized pipette, inoculated into a tube of plain blood serum, and incubated at 37° C. Smears were also made from the bottom of the centrifuge tube. These, like smears from the uncentrifugalized serum, showed only a quantity of fibrin and small numbers of red and white blood cells, probably blood flowing from nick in the capsule. The inoculated tube showed no visible growth after twenty-four hours; the surface of the serum was bathed with the water of condensation. Twenty-four hours later a plentiful growth of discrete, colorless, pinpoint colonies appeared in pure culture over the whole surface.

The remainder of the serum, about ℥iss, was transferred to a sterile Florence flask and incubated at 37° C. Four days later a drop from this flask showed presence in small numbers of an organism, morphologically the same as cultivated from centrifugalized portion, but clumped and immotile:

2. *Tissue.* This consisted of five or six small bits of rather lipomatous nature and not very vascular. The most vascular-looking bit was snipped several times with a pair of sterile scissors, quickly transferred with sterile forceps to a tube of plain blood serum, and incubated at 37° C. After twenty-four hours no growth was evident, and surface was bathed; after forty-eight hours it showed a growth identical with that from the centrifugalized serum, and examination showed presence of the same organism in pure culture. The cultural and morphological characteristics are later described in outline.

The remainder of the tissue was placed in 10 per cent. formalin for histological examination. Cut sections showed no peculiarities other than described in the introduction. The organism isolated does not stain by Gram's, but sections stained with polychrome methylene blue and eosin show the presence of the bacillus in very small numbers in the tissue.

Animal experiments are recorded later.

CASE III.—Annie M. B., Massachusetts; aged forty years; single; music teacher. Admitted December 17, 1904. N. E. Baptist Hospital, Dr. Goldthwait.

Complaint. Pain and swelling in many joints, especially hands and elbows.

Family History. Mother died of cancer of stomach. Father died fourteen years ago of typhoid fever. Definite "rheumatic" history on the part of two maternal aunts, both being on crutches and crippled in many joints for ten years and twenty-five years, respectively.

Personal History. Measles and mumps in infancy. Typhoid fever fourteen years ago, at same time with father. No history of traumata or early joint troubles. Never robust, but always in fair health until attack of typhoid fever.

Present Illness. Began at age of twenty-six years, seven weeks after full convalescence from a typhoid fever unaccompanied by complications. An acute swelling developed suddenly in both wrists, coming and going irregularly. In the next few years various other joints became involved, especially of hands, elbows, knees, and feet, with occasional pain referred to hips. At various times the swellings have been very considerable, hot, red, and painful. They were never aspirated. Twelve years ago hands were so troublesome that work (stenography) was impossible. Much improved a year later, and for five years grew steadily better. An attack of influenza (?)

four years ago seemed not to affect joint conditions. Eighteen months ago had erysipelas of face, after which no trouble until a year later, when the frontal sinus was opened on account of a progressive swelling in left orbital region; character of pus not determined. Since that time, however, all joints have been worse, particularly in the hands, and the trouble has since appeared in the shoulders. The general health at present is fair, but the patient is in a nervous condition.

Physical Examination. Fairly well developed, poorly nourished, pale. *Heart* and *lungs* negative. *Abdomen* negative; spleen and liver not palpable. *Glands* slightly enlarged in neck and in both axillæ; epitrochlear glands not palpable.

Special Examination. Both sternoclavicular joints tender; slight swelling about both maxillary joints, and movements painful; spine apparently not involved. *Shoulders:* the right allows normal motion, but with much crepitation; the left shows same condition, but motions are all guarded. *Elbows:* both show normal amount of flexion, but stop short 20° of complete extension. *Wrists* and *hands:* distinct swelling of practically all the metacarpophalangeal and several interphalangeal articulations, with slight amount of ulnar deflection of both hands. Hips apparently not involved. *Knees:* motions somewhat guarded and painful in both joints; outlines practically normal. Both feet and ankles negative.

x-Ray: A good negative of both hands and wrists shows practically no alteration from normal in either bone or cartilage.

December 22, 1904. The two most swollen joints of the hands—the right middle metacarpophalangeal and the left middle proximal interphalangeal—were aspirated for bacteriological purposes.

23d and 25th. 6 c.c. and 8 c.c. of Aaronson's antistreptococcic serum injected into thigh muscles.

28th. Has been having evening temperature of 100° to 100.5°, with morning remissions to normal; pulse, 100; respirations, 24. To-day temperature rose to 101.4°; pulse, 120; respirations, 26. There was pain in right nipple line over liver. Transferred to Dr. Badger, account of pulmonary conditions.

30th. The picture is clinically of pneumonia, but examination is negative; some few friction rubs over base of right lung in front.

Leukocytes, 24,000. Urine negative. Respiration short, painful, shallow. No sputum.

January 1, 1905. Bronchial respiration over left base, behind.

3d. Pneumonia fully established in left lower lobe. Heart free.

6th. A to-and-fro pericardial rub without signs of fluid.

25th. Three ounces clear fluid withdrawn from pleural cavity. No culture made.

February 4th. Delayed resolution slowly clearing. Heart conditions have cleared. General condition much better. Joint symptoms have improved in a remarkable way.

March 11th. Lung is not wholly cleared; a little bronchial respiration still heard at left base, otherwise resonance and respiration good throughout. There has never been any sputum. The highest temperature was 103.2° on January 1st.

Discharged by Dr. Badger, well of pulmonary conditions* and with joints in better condition than for months.

Bacteriological Report. As noted above, one joint of each hand was aspirated under aseptic precautions, several days before onset of pulmonary symptoms. From each joint one small drop of serum was obtained, and from each one plain blood-serum tube was inoculated, and incubated at 37° C. Unfortunately no smears were made from the needle points. At the end of two weeks one tube was discarded, being sterile.

The tube inoculated from the right middle metacarpophalangeal joint showed no visible growth at end of twenty-four hours; surface was bathed with water of condensation. Twenty-four hours later a fine growth had appeared over surface of medium—colorless, glistening, pinpoint colonies in pure culture. Subcultures were made on various media. The organism is described in the outline later.

Animal inoculations are also recorded later.

The following case differs from the preceding three in being one of typical acute articular rheumatism.

Case IV.—Solomon K., Russian Hebrew; aged nineteen years; papermaker. Admitted January 9, 1905. Carney Hospital, medical service, Dr. Minot.

Complaint. Knees painful.

Family History. Not obtained.

Personal History. "Rheumatism" twice before, last attack one year ago. Denies all acute infectious and venereal diseases.

Present Illness. Began December 14, 1904, with pain in ankles and left elbow. Three days later admitted to Boston City Hospital with temperature of 102.5°, pulse 120. Throat was found normal; no glandular enlargements. The left elbow was tender but not red; the right ankle and foot were tender, red, and swollen. Was given antirheumatic treatment, and being somewhat improved was discharged, January 5, 1905, to United States immigration authorities. January 9th admitted to Carney Hospital, saying he had caught cold the day before and could not walk because of pain in knees.

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* Bannatyne,[7] speaking of the arthritic type to which this case belongs, says (p. 27): "I find that about 3 per cent. of my cases developed either pneumonia or pleurisy during the time they were under my care, and about 17 per cent. developed endocardial or pericardial conditions after the onset of the disease."

MORPHOLOGICAL AND CULTURAL CHARACTERISTICS.

	Bacillus No. 1. Case 1.	Bacillus No. 2. Case 2.	Bacillus No. 3. Case 3.	Bacillus No. 4. Case 4.
Morphology: shape .	Long plump rods, with slightly rounded ends.	In first cultures diplococcoid, but after transplantation — plump rods of moderate length, with slightly rounded ends.	Pleomorphic.[2] Lanceolate diplococcoid forms; on favorable media single and diplobacilli, with rounded ends, generally lying in parallel clumps.	Long, plump rods, with slightly rounded ends.
arrangement .	Single, in pairs or in long chains; no true branching forms found.	In pairs chiefly; also single forms and short chains; no true branching forms found.	……………………………………	Single, in pairs, or in long chains; no true branching forms found.
size[1] . . .	Width 0.5-0.68 μ; length 1-4.9 μ; averaging 1-2 μ.	Width 0.6 μ; length 1-2.4 μ.	Width 0.6-0.8 μ; length of elements 0.7-1 μ; length of pairs 1.08-2.36 μ.	Width 0.72-0.76 μ; length 1.6-4 μ; averaging 1.5-2.5 μ.
capsule . .	None demonstrated.	None demonstrated.	None demonstrated.	None demonstrated.
spores . . .	Clostridium type; readily produced in old cultures.	Clostridium type; considerable numbers in 8-day blood-serum cultures.	None demonstrated.	Clostridium type; great numbers in 8-day bouillon cultures.
Motility . . .	Actively motile.	Actively motile.	Non-motile.	Actively motile.
Staining properties .	Stains readily with aniline dyes, and by Gram's.	Stains readily with aniline dyes, decolorized by Gram's; occasional polar granulation in old cultures.	Stains readily with aniline dyes, and by Gram's.	Stains readily with aniline dyes, decolorized by Gram's.
Cultural chars . .	Facultative anaërobe.	Facultative anaërobe.	Aërobic, practically no anaërobic growth.	Facultative anaërobe.
blood-serum, 37° C.	Grows vigorously, in 48 hours covering surface of medium and water of condensation with a thick, tough, corrugated pellicle of pale rose color; liquefaction of medium fairly rapid; not checked by icing.	Delicate growth as raised, viscid, colorless thin line; discrete colonies are round, raised, flat, colorless, pin-point, increasing to pin-head size in 2-3 days; no further increase.	Individual colonies same as of bacillus No. 2, but growth even less marked along streak, and not progressive.	Very vigorous growth, liquefaction beginning in 12 hours, and producing deep, viscid, yellowish furrows; a heavy, smooth, white pellicle rapidly covers water of condensation; discrete colonies minute, round, raised, moist, whitish, translucent, quickly fusing.
plain agar, 37° C.	Streak: grows well, in 24 hours showing a broad, elevated, white streak with moist, wrinkled surface, increasing but little after 48 hours, becoming powdery; individual colonies are minute, colorless dew-points, rapidly fusing. Stab: fair continuous growth, not increasing.	Streak: same as on blood serum at 24 hours, colonies later becoming ivory white. Stab: fair filamentous, continuous growth by third day, not increasing.	Streak: only a few smooth, round, flat, slightly elevated, discrete colonies, colorless, of pinpoint size, slowly increasing to diameter of 2 mm. and becoming whitish and crenated. Stab: very faint growth in depths.	Streak: after 24 hours, a slightly elevated, ivory white, broad streak, with irregular, smooth border; heavy, smooth, white pellicle over water of condensation; after 48 hours little change; no liquefaction. Stab: moderate, continuous, white growth after 24 hours, soon producing small, tuberous offshoots.

potato, 37° C.	At 24 hours a good growth; several large, viscid, white globules along an ill-defined, faint, pinkish streak, suggesting appearance of watermelon fibre; at 48 hours globules are collapsed, a wide-spread, rose colored growth in dew-point globules; later develops a blood-red color, not diffused.	Grows with difficulty, producing no visible changes.	Limited growth; moist, raised, whitish, almost invisible; typical forms in smears from scrapings.	At 24 hours raised, moist, sticky, lemon-colored growth of considerable vigor, in broad, irregular streak; medium slightly darkened; by fourth day growth has increased and become whitish, potato discolored brown; no further advance.
alkaline bouillon, 37° C.	Quickly becomes turbid; small waxy globules float on surface, later coalescing to form a firm pellicle, like honeycomb, over the whole surface.	Grows well, producing general turbidity in 24 hours.	Grows fairly well, producing slight general turbidity, and small amount of white, granular sediment.	Marked, rapid turbidity; by third day waxy scales float on surface, later uniting to form a dry, friable white pellicle.
litmus milk, 37° C.	Pellicle formed as on bouillon, finally firm enough to resist on inverting tube; slight alkaline reaction by fourth day, followed by bleaching: gradually acidified after 10 to 14 days; no definite clot.	Grows well, a faint alkaline reaction developing slowly.	Grows well, a faint alkaline reaction developing slowly.	A firmer pellicle than on bouillon; alkaline reaction on second day, followed by bleaching; turns acid in 7 to 10 days, with late formation of clot, digested slowly.
glucose gelatine, 20° C.	Stab: infundibuliform liquefaction, gradually reducing surface to level; fair growth in depth; no gas; pellicle faint rose in old cultures.	Stab: slowly produces slight, brown, granular growth in upper half, not advancing; no gas; no liquefaction.	Stab: barely perceptible whitish growth throughout stab, not progressing; no gas; no liquefaction.	Stab: infundibuliform liquefaction, gradually reducing surface to level; thick, sticky pellicle; no gas.
His' semisolid, 20° C.	No gas.	No gas.	No gas.	No gas.
Dunham's peptone, 37° C.	No indol.	No indol.	No indol.	No indol.
at 20° C.	Grows well on blood serum, but without pigment, and less vigorously than at 37° C.	Grows fairly well on blood serum, but soon dies out.	Grows weakly on blood serum.	On blood serum same as at 37° C., but more slowly.

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[1] Fresh twenty-four-hour bouillon cultures stained with Loeffler's methylene blue.

[2] The unusual forms are described under section on "Animal Experimentation."

Physical Examination. Well developed and nourished. Pharynx congested. *Lungs* negative. *Heart* impulse diffuse over large part of præcordia; apex in fifth space, 11 cm. from midsternal line, not enlarged; sounds regular; blowing systolic murmur over whole præcordial area, loudest at apex, transmitted to axilla and back; second pulmonic sound accentuated; diastolic murmur, heard loudest at base in pulmonic area. *Abdomen* negative; liver and spleen not felt. *Knees*: Right shows but little swelling, not red or hot, moderately sensitive to pressure. Left somewhat swollen and warmer than right, but less sensitive. Both patellæ free, but motions are guarded. Aside from the knees the second phalangeal articulations of the middle fingers in both hands and the right wrist-joint were swollen.

Temperature on admission 100.5°. *Pulse*, 90. *Urine*, negative. *Blood:* Hæmoglobin, 90 per cent.; red blood corpuscles, 5,200,000; white blood corpuscles, 11,600.

The treatment is not of interest in this connection. By January 22d the joint conditions were considerably improved, but still complained of pain in elbow. The temperature, never higher than 100.5°, came down slowly. To escape the immigration officers the patient suddenly disappeared from view, January 29th.

Bacteriological Report. January 12th. Both knee-joints were aspirated under ethyl-chloride anæsthesia, after scrubbing with 80 per cent. alcohol. They had previously been prepared as described under the heading "Technique." From the right knee about two drops of serum were obtained and inoculated into a tube of plain blood serum; unfortunately not enough was left to inoculate a second tube. Smears were made from the needle point. The same description applies to the left knee. The smears were stained with gentian violet, and with Loeffler's methylene blue; a prolonged search revealed nothing but large mononuclear leukocytes in small numbers.

The tubes showed no visible change after incubation for eighteen hours; the surfaces of media were bathed with the water of condensation. Forty-eight hours after inoculation* pure cultures of the same organism had developed in both tubes, described subsequently in the outline.

Animal inoculations were carried out and are recorded in a later section.

CHARACTERS OF THE ORGANISMS FOUND IN THE FOUR POSITIVE CASES.

These are described in considerable completeness, not because the organisms themselves are of special interest, but for the better comparison with others they may resemble and with others found in cases of the same clinical types. It has not been possible to identify any of them with previously described organisms; in the attempt to do so reliance was placed chiefly in Chester's Manual.* (See tables pages 1066 and 1067).

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* This forty-eight-hour incubation period does not suggest contamination; it was later observed in all cases in which organisms were recovered from joints of inoculated animals.

ANIMAL EXPERIMENTATION.

Value of Evidence Afforded by Animal Experimentation. Three facts of importance here are to be deduced from the work done in this direction:

1. The well-established difference that various animals display, (*inter se* and compared with man), in their reactions to many organisms.
2. The greater resistance in general shown by animals as compared with man, more particularly in the case of organisms of slight pathogenicity.
3. The ability of a variety of *entirely distinct organisms* to produce in the joints of animals *changes indistinguishable clinically or pathologically*. This is well illustrated by the comparison of results obtained by Shaw[8] and by Cole,[9] in their milder cases, with those in my own series. Shaw worked with an organism from acute rheumatic joints. Cole employed virulent strains of streptococcus pyogenes.

From this it follows that:

1. The exact reproduction in animals of the lesions in human joints is, *a priori*, not to be expected.
2. Failure to produce *any* well-marked joint lesions is not to be interpreted as evidence of particular significance.
3. Positive results are no more than suggestive.

Report of Experiments.

In this work rabbits were inoculated, some intravenously and some directly into the joint. For the latter purpose the knee-joint was used; the left side was selected for experimentation, the right (with one exception, No. II., Case 1) was reserved for control. Both joints were shaved for comparison, and frequent observations were made both of local and general conditions. It may be said here that in no case did the general condition appear influenced by the treatment. Moreover, the animals inoculated intravenously never showed the slightest signs of articular disturbance, although large doses were administered in three cases, and in the fourth (No. IV., Case 1) 1.5 c.c. was injected, and the organism used had been passed several times through joints in which it excited an acute process.

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* A Manual of Determinative Bacteriology, Macmillan Co., 1901.

Case 1. Rabbit I. Left knee.

October 5th. Received an initial dose of ♏viij bouillon suspension of a fresh blood-serum culture.* Only a transient inflammatory reaction followed, but after six weeks there gradually developed a periarticular thickening with signs of fluid in joint. At end of two months this condition was well established. Nine days after inoculation a pure culture was recovered by aspiration.

December 16th. Reinoculated with ♏ij bouillon suspension from forty-eight-hour blood serum; the organism used was from a pure culture recovered from joint of Rabbit II. at autopsy.

The chronic condition became decidedly more marked, and joint was much distended with fluid; there was a persistent limp.

January 19th. Thirty-four days after last injection animal was chloroformed. *Left knee:* Capsule considerably distended and thickened; typical villous proliferation of synovial membrane; no acute inflammatory signs; bone apparently normal. Capsule contained about 2 c.c. of tenacious, whitish fluid containing a few flakes, which smears showed to be of nature of mild exudate; no organisms found in smears. Pure culture of original organism cultivated from joint fluid. The right knee appeared normal, as did all the internal organs. Joints were preserved as specimens.

Rabbit II. Both knees.

October 7th. *Right knee* inoculated with ♏viij from a pure blood-serum culture from joint of Rabbit I. (aspirated twenty-four hours after first injection).

10th. *Left knee* received ♏x suspension from recent blood serum culture. Four days later a pure culture was recovered and smears showed presence of a mild exudate, a few bacilli appearing in pairs. No clinical signs appeared in either joint.

27th. Died as result of an old process in lungs. Externally both joints appeared normal. The *right* showed only slight villous changes; smears and culture negative. The *left* contained an excess of fluid of exudative character, as shown in smears; there was distinct synovial thickening with congestion and, in places, typical villi. A pure culture was recovered from this joint. In paraffin sections from the synovial membrane histological changes were found, differing in no essential detail from those in the original human joint. Sections stained by the Gram-Weigert method showed the presence of organisms similarly situated in the tissues and identical in appearance with those found in the human villi. The liver showed small foci of coccidial disease. Both lungs contained large abscesses; the left was converted into a single large cavity containing about ℥ss of thin white pus. The nature of the latter process was not determined, but it clearly had nothing to do with the joint conditions and was evidently the cause of death.

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* In the following notes, unless otherwise stated, it is to be understood that suspensions of twenty-four-hour blood serum were used for inoculations.

Rabbit III. Left knee.

October 12*th*. A pure culture from the joint of Rabbit II. was used; ♏viij were injected. A slight, transient, inflammatory reaction followed; a slight limp developed later.

December 16*th*. Reinoculated with ♏ij from forty-eight-hour blood-serum subculture of organism isolated at autopsy from left knee of Rabbit II. Result slight.

24*th*. A final inoculation with ♏viij suspension from forty-eight-hour blood-serum culture, taken from joint of Rabbit I., resulted in a gradually increasing swelling, without acute signs, but causing limp. Eighteen days after inoculation a pure culture was recovered from the joint; smears showed existence of a considerable exudate.

The clinical signs had all disappeared at end of four weeks, but some capsular thickening persisted.

March 21*st*. Three months after last injection, chloroformed. *Left knee* showed merely a moderate degree of villous proliferation; smears and cultures negative. Joint saved as specimen. The right knee and internal organs appeared normal, and cultures from the heart blood, spleen, liver, and kidney were sterile.

Rabbit IV. Vein of ear.

January 18*th*. A twenty-four-hour bouillon subculture from joint of Rabbit III. was used; ♏xv were injected intravenously. No effects observed.

24*th*. 1.5 c.c. of a twenty-four-hour bouillon from same source injected. No effects whatever. Animal was still well until April 5th, when used for other purposes.

Case 2. Rabbit I. Vein of ear.

January 24*th*. 2 c.c. of twenty-four-hour bouillon culture, intravenously; no effects.

February 1*st*. Subcultures were made on blood serum from organism recovered from joint of Rabbit II. The growth on four twenty-four-hour blood-serum tubes was suspended in 5 c.c. of bouillon and injected into the vein. No effects. The animal is still well after eleven weeks.

Rabbit II. Left knee.

January 24*th*. ♏iv of twenty-four-hour bouillon caused only mild inflammatory signs, gone in forty-eight hours. The only time the organism was recovered from the joint was four days after this injection; it grew in pure culture; a very few organisms were also discovered in the smear from the joint fluid.

30*th*. Injected ♏iv suspension from forty-eight-hour blood-serum culture recovered from same joint. A slight reaction with moderate swelling, gone in two days.

February 16*th*. ♏v injected.

26*th*. ♏x injected.

In all, four inoculations were made but a satisfactory reaction was never obtained.

March 14*th*. Seven weeks after first inoculation, animal chloroformed. *Left knee* appeared practically normal, save for a few pale villi below the patella. Paraffin sections were made of these and the tissue was found lipomatous, in this respect resembling parts of the human tissue in this case. In one place a deposit of lime salts was found in the capsule. Staining with polychrome methylene blue and eosin failed to show presence of any organisms. There was no picture of acute infiltration, as in most of the sections from the human joint. Smears and cultures from this joint were negative. The right knee was normal, also the internal organs, cultures from which remained sterile.

Case 3. Guinea pig. Subcutaneous injection.

Of a twenty-four-hour bouillon culture $\frac{3}{4}$ c.c. was injected beneath skin over abdomen. Three weeks later a soft enlargement of glands in both groins appeared. No constitutional disturbance could be made out, and after three months animal was alive and well.

Rabbit A. Left knee.

January 19*th*. ♏iij of twenty-four-hour bouillon provoked little reaction.

28*th*. ♏vij from twenty-four-hour blood serum caused considerable swelling and some limp; practically normal by the fourth day.

February 8*th*. ♏x caused considerable swelling and some limp. Aspiration after five days showed presence of exudate and active phagocytosis in joint; culture sterile.

20*th*. Only a periarticular thickening remains. ♏iij injected. (Any effects of this inoculation were obscured by the development of an abscess located near, but outside the joint, having apparently nothing to do with the injections. Similar abscesses were present beneath the skin in other places before the injections were begun; the condition is very common in rabbits. The abscess in question disappeared in about ten days). A polar-staining bacillus, in pure culture, was obtained from the extra-articular abscess. As it was decolorized by Gram's it cannot be identified with the Gram-staining organism found later in sections from the synovial tissue.

March 2*d*. ♏x injected. No acute signs, but a considerable capsular distention and limp resulted, persisting until animal was killed.

The organisms were never recovered from the joint, though several attempts were made. As early as forty-eight hours after injection all organisms appeared to have been included by the phagocytes.

20*th*. Two months after first inoculation, animal chloroformed. The right knee and the internal organs appeared normal; cultures from the latter remained sterile. *Left knee* contained about ♏vij of tenacious grayish exudate, from which cultures were sterile. Fibrous capsule normal, but there was a considerable uniform thickening of synovial capsule. A few minute villi hung by thread-like pedicles from the ligamentum mucosum; a few also projected from above the patella. These latter were sectioned in paraffin and stained by the Gram-Weigert method. Histologically, sections showed a moderate synovial thickening with presence, in considerable numbers, of the new tissue-forming cells; there was only a moderate degree of infiltration with small round cells and polymorphonuclears. Occasional sharply stained bacilli were found singly and in pairs. The latter were identical in size and appearance with certain forms occurring in the cultures from this case.

The following experiments were made with the view of identifying, if possible, these organisms with the ones injected—pleomorphism on artificial media having already been observed in the latter.

Rabbit IV., Case 1, was used, and on two different occasions 0.5 c.c. and 1 c.c. from twenty-four-hour cultures on blood serum were injected into the left knee-joint. Aspiration after twenty-four hours and eighteen hours, respectively, showed practically all the organisms included in phagocytes and incapable of staining by Gram's; cultures remained sterile. 25 c.c. of cloudy forty-eight-hour bouillon was then injected into the peritoneum, and after six hours a small quantity was withdrawn. In smears only a few organisms, and these of short forms, were found; many phagocytes appeared but the disappearance of the organisms seemed mainly due to bacteriolysis. Typical pure cultures grew in discrete colonies on blood serum.

Rabbit B. of this case was then similarly injected with 50 c.c. intraperitoneally. Two and three-quarter hours later a small quantity was withdrawn. Smears showed same picture as above, short pairs staining by Gram's being found free and in the leukocytes. Typical pure cultures grew in discrete colonies on blood serum.

After a few days both rabbits showed little sign of infection; it is too early to make any further report.

From the pure cultures in the last two cases smears were made on second and third days, and stained by Gram's. The majority of organisms were short diplobacilli; small coccus forms also occurred, and a small number of single long rods. The latter were measured with the micrometer and compared with the similarly stained organisms found in the tissue from Rabbit A. Here are the comparisons:

From cultures on blood serum: length in four cases: 1.9μ, 2.4μ, 3.1μ, 3.7μ.

From stained sections of synovial membrane: length in two cases: one diplobacillus, elements 1.3μ, pairs 2.8μ; one single rod, 3 (3.0μ). One or two longer forms in the tissues could not be measured, not lying in a horizontal plane.

Without cultures from the tissue the proof is incomplete, but the failure to obtain any growth from fluid aspirated on six different occasions speaks for the singleness of the infection.

Rabbit B. Vein of ear.

January 28th. A sterile water suspension of growth on four twenty-four-hour tubes of blood serum, intravenously, produced no noticeable effects. Ten weeks later this animal was used for intraperitoneal inoculation as noted above.

Case 4. Rabbit I. Left knee.

January 19th. ♏v of twenty-four-hour bouillon caused a fair inflammatory reaction with limp, lasting six days.

28th. ♏vij of twenty-four-hour bouillon caused less acute inflammatory change but more swelling and limp.

February 5th. ♏viij suspension of pure culture recovered from joint, and grown forty-eight hours on blood serum, produced a good local reaction with limp, and persistent swelling.

16th. ♏ij as above from a recently recovered pure culture. No acute reaction.

28th. Swelling about gone. ♏xij caused a transient acute reaction, followed by a progressive swelling and limp, clearing after ten days.

March 18th. Eighteen days after last inoculation, animal chloroformed. The right knee and internal organs were normal. Cultures taken from the liver and spleen showed a few colonies of cocci, not pyogenic, and clearly not related to the experimental infection. *Left knee* contained slight serous exudate, from which the bacillus, in pure culture, was grown, and smears from which showed rare organisms, free and in the leukocytes. The synovial membrane was not congested, but bore patches of fine villi, a portion of which were taken for examination. A curious body, of the size, shape, and appearance of a small cantaloupe seed, lay in lower end of the lateral pouch outside the external condyle. It was attached by a long, thread-like pedicle to the inner side of the opposite condyle, where the synovial membrane had a fibrinous coating. Histologically, it was found to be organizing exudate. The villous specimen sectioned in paraffin, and stained with polychrome methylene blue and eosin, presented a beautiful histological picture, comparable to that in Case 1, but no organisms could be found after long search through many preparations.

Rabbit II. Vein of ear.

January 28th. 4 c.c. of twenty-four-hour bouillon.

February 6th. 3.5 c.c. suspension containing twenty-four-hour product of four tubes inoculated with pure culture from joint of Rabbit I.

After ten weeks no effects whatever have been detected.

III. Interpretation of Results.

This necessitates a consideration of the reports of other workers in this field. The findings in cases of acute articular rheumatism are not included here.

BACTERIOLOGICAL REPORTS OF OTHER OBSERVERS.

1. *Schüller.* This evidence is considered first, as it is the most extensive and applies without question to the described class of cases.

His first report[9] was in 1892, when he mentioned finding constantly, in cut sections of tissue from the joints, the same organisms described in later papers.

1893.[10] By tapping joints (with cannula, allowing serum to drop directly on media in tubes and plates) he obtained the same bacilli found previously in histological sections. They are described as *short, plump rods, showing polar granulation* distinct from spores; the latter appear, however, in old cultures. Rods measure 0.75μ to 0.99μ x 2.24μ to 2.76μ, and stain by ordinary methods, though easily decolorized; no note here or elsewhere of Gram's method. Grew well at 25° C. in dark. In gelatin stabs, small white granules along course of puncture, going on to liquefaction; plates show whitish-gray points. On agar, similar plaques; the same on potato. Cultures ten to twelve months old were revived and proved infectious. Inoculation into rabbits' joints of 0.5 to 1 gm. caused marked swelling of permanent character and persistent limp. Animals were killed at end of two months, prior to which original organisms were recovered from inoculated joints. Pus was never found in the experimental joints; synovial membrane bore, in places, pale and brownish villous fringes, sections of which were shown to contain the organism injected. The uninoculated joints displayed no changes. Subcutaneous injections caused no suppuration, only slight local induration, but doses of 0.5 to 1 gm., it is said, were fatal in twenty-four hours. Injection of like quantity into joint produced nothing like this fatal picture.

1896.[11] A quick method is described for demonstrating the organisms in human tissues. At operation, when the fringes protrude through the wound, they are washed off with sterile water or $HgCl_2$, split open with a fresh knife and a sterile glass slide drawn across the newly cut surface. Smear is air-dried and stained with carbol fuchsin.

1897.[3] In sixteen arthrotomies, in cases of the type differentiated, in smears from the freshly cut villi (after method described above), and later in sections from these tissues, the bacillus was constantly demonstrated, generally easily, as the organisms are actually in the tissues and much less frequently free in the joint fluid. In aspirating the needle should be thrust, he says, not into the joint cavity but into the synovial tissues, where the organisms actually are. Of twenty-three aspirations, six were negative. In the pathological tissues the organisms are found mostly at the site of the greatest changes. Cocci often appear together with the bacilli, both in aspirated material and that obtained at operation; in one aspiration cocci only were obtained. These appear identical with the pyogenic cocci and are not regarded as playing any important role, certainly not a causative one. A comparison is made with cases of joint tuberculosis, where the tubercle bacillus is often found in small numbers, while pyogenic cocci are abundant. The present bacillus is not easily demonstrated in sections, because so readily decolorized.

A later paper,[5] in 1900, adds nothing bacteriologically.

2. *Bannatyne,*[7] *Wohlmann and Blaxall,*[12] 1896. Next to Schüller's this is the most complete bacteriological report bearing on our subject. It is therefore necessary to examine carefully the nature of the cases from which the evidence is deduced.

It is clearly emphasized (p. 79[7]) that cases of the hypertrophic type of arthritis deformans are to be excluded, and that it is from certain acute polyarticular cases only that the organisms were isolated. These cases are defined in pp. 91 and 92, from which the following is quoted: "Dr. Still, in Clifford Allbutt's *Medicine*, says there is in children a disease which presents important differences both in its clinical symptoms and morbid anatomy, as well as one which is clinically analogous to the rheumatoid arthritis of adults. The first type of the disease is characterized by chronic progressive enlargement of the joints . . . the joint thickening affects the tissues round the joints, rather than the bones or cartilages. . . . The pure rheumatoid arthritis in children he considers to be characterized by bony thickening and lipping about the joints. . . . Now, his description of the first class corresponds with my description of what we see in adults in the acute form of the disease, and also his second with the chronic form."

It is from adult joints of the first type, acute at the onset but developing permanent changes not involving bone or cartilage, that the following bacteriological evidence was obtained. Further descriptions (pp. 93 and 94[7]) bear out the conviction that Bannatyne is here dealing, in part at least, with the *polyarthritis chronica villosa* of Schüller, with whose work, and that of Chauffard and Ramond,[13] he compares his own bacteriological results.

To turn to these now, as summed up in the conclusion of Blaxall's report:[12]

"1. In the synovial fluid in eighteen cases of rheumatoid arthritis an organism has been demonstrated, which is constant in its characteristics.

"2. The organism is a minute bacillus, exhibiting marked polar staining. It is difficult to stain and easily decolorized.

"3. The organism can be grown in culture media, and presents striking characteristics. In beef-broth it gives the appearance of gold dust; and on agar-agar and serum its growth is almost invisible.

"It does not grow on nutrient gelatin at ordinary temperature.

"4. It is present in the blood of severe cases.

"5. It has not been found in the synovial fluid from distended joints due to other causes."

Two years later Bannatyne[7] states that in the few sections he was able to obtain, the same bacillus was found in the cartilages, synovial membrane, and periarticular tissues.

A special method for cultivation and an elaborate technique for staining were employed. The organism is described as averaging $0.6\mu \times 2\mu$, not occurring in chains, non-mobile, decolorized by Gram's, and in general requiring special care in staining. For further accounts of cultural characteristics, etc., reference should be made to Blaxall's report.[12]

Inoculations of mice, guinea-pigs, and rabbits were without results.

The bacillus is differentiated from Schüller's. It is mentioned in comparison with that found by Chauffard and Ramond, which, it is incorrectly stated (p. 83[7]), they "cultivated" from the synovial fluid.

Though a firm believer in the infectious origin of these cases, Bannatyne is uncertain as to the role played by the organism he has found.

3. *Von Dungern and Schneider,*[14] 1898. This is an account of a single case, very like, except for its fatal result, to my Case 1.

Man, aged forty-four years; acute polyarticular attack, subsiding after five months, leaving heart lesion; complete freedom for twelve years, when a second attack left him with permanent joint changes and some spinal rigidity; these conditions were still present five years later, when death occurred from inanition. At autopsy, characteristic changes were found in the joint synovial membranes, but with thinning of cartilage.*

The bacteriological report is of interest. It is based on a study of: 1. Aspirated fluid from finger-joints and blood from vein of arm (taken six months before death). 2. (Taken eighteen hours after death), fluid from several joints, heart blood, spleen, liver, kidneys, mucus from gall-bladder. Nothing was obtained from blood, spleen, or kidneys.

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* On the basis of this latter fact the authors thought to distinguish this case from the type described by Schüller. It has already been pointed out, however, that such changes are not uncommon as secondary to long disuse or unusual severity of the local process, both of which features were present in this case; the patient had been completely bedridden for seven months before death.

In smears a small diplococcus was found from the gall-bladder and cultivated on various media. The same organism was cultivated from the joint fluid and the liver. Morphologically, it much resembled diplococcus lanceolatus, grew in pairs, singly, or in chains up to ten, the pairs being 0.6μ wide x 1 to 2μ long, involution forms occurring. On agar small, discrete, transparent colonies were produced; on potatoes a white, granular growth, not elevated; on glucose agar after twenty-four hours a heavy confluent growth; milk acidified and coagulated in twenty-four to forty-eight hours; viability on artificial media demonstrated for at least three months. It was not identified with any previously described organisms. The joint lesions were reproduced by intra-articular inoculation in rabbits; importance was attached to the destructive changes* produced in the cartilages (not caused by Schüller's organism nor by control injections of pyogenic and other cocci, although villous and purulent conditions resulted from the latter). The diplococci were recovered and cultivated four to six weeks after injection.

From the liver and gall-bladder of this case, beside the diplococci, one other organism was found, from its morphology, cultural characteristics, and pathogenicity for animals, probably bacillus coli. From the joint fluid taken intra vitam a non-pathogenic coccus also grew; from that obtained postmortem there occurred, together with the diplococcus, a non-pathogenic bacillus.

The following conclusions were reached:

Not much importance is attached to these other organisms, yet it cannot be proven that the last two did not take part in the joint processes. Lesions once produced in joints render the latter favorable seats of infection. A good illustration is our finding there organisms of ordinarily such slight pathogenicity. It is possible that the diplococcus infection itself was not established by one invasion, but by successive attacks, these organisms being particularly abundant in the chronically diseased gall-bladder.

4. *Chauffard and Ramond,*[13] 1896. In a communication entitled "Des Adénopathies dans le Rheumatisme Chronique Infectieux" descriptions are given of seven cases. Excepting two that are probably of gonorrhœal origin these are evidently of Schüller's type. In all cases the anatomically related glands were distinctly enlarged; in two, valvular heart lesions existed. The bacteriological evidence is admittedly slender, and was sought in but one case. The joint fluid was twice aspirated and inoculated directly into tubes and animals, with negative results. The two

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* The little reliance to be placed in inferences drawn from lesions produced in animal joints has already been referred to.

epitrochlear glands were extirpated with strict asepsis. Of each a part was triturated and inoculated into culture tubes and various animals, with negative results; in histological examination of the remaining parts no organisms were found. Smears previously made from cut surfaces of the glands, and from the joint fluid, showed apparently the same organisms—short, fine diplobacilli, staining with the ordinary dyes, and not decolorized by Gram's.

Because of the frequent reference made to it by various authors, this report has been detailed to show its admitted lack of bacteriological value. It will not be referred to again.

5. *Bouchard and Charrin,*[15] 1891, 1894. These reports are also frequently referred to. The finding of pyogenic cocci in twenty-two cases of chronic joints is related, but the bare statements to this effect carry with them no conviction and do not require our consideration.

DEDUCTIONS.

It is not justifiable to base an opinion as to the etiology of a large group of cases, however much they may resemble each other clinically, upon a study of so few of its members. So much incredulity has been shown by the profession in general, with regard to the bacteriological reports previously made in rheumatic cases of various types, that pains have been taken in this paper to go into much detail.

Infectious Polyarthritis Chronica Villosa.

Case 1. The chain of evidence, so far as it is to be considered as such, is complete. The organism was isolated in pure culture from one of several joints in which the process had been recently active, and clinically typical. Histologically, it was found alone in the synovial tissue, included in the cells in an evident causal relationship. It was cultivated on artificial media. Injected into the joints of rabbits, it there provoked both acute and chronic processes, in nowise differing clinically or pathologically from those in the human joint. The organism was isolated repeatedly in pure culture from the animal joints, and sections from the tissues of the latter showed the presence in small numbers of this organism alone, similarly situated to those in the human tissue. Subcutaneously and intravenously moderate doses of exalted virulence were without effect.

Case 2. The organism in this case was isolated in pure culture, both from the synovial fluid and from the tissue, and grown artificially. Its presence was demonstrated in the human tissue, as in the preceding case. Though recovered in pure culture from the animal joint into which it had been inoculated, it failed there to produce any marked changes. Large doses intravenously were without effect.

Case 3. From one of two joints which were aspirated an organism was obtained in pure culture, under conditions that left little doubt that it played some role in the morbid process. Animal experimentation produced the same satisfactory results as in Case 1. Large doses intravenously proved harmless.

From each of these three cases a single different organism was isolated, apparently capable of considerable resistance under artificial conditions.

The findings in these cases differ from those of Schüller, who found in his own cases the same organism constantly. Bannatyne likewise, in the same type of cases, constantly found a single organism, but it was not Schüller's. It is impossible to explain the constancy of Schüller's results or of Bannatyne's. It is clear that they worked with the same type of cases as my own.

From the reports of previous observers, then, we should be inclined to believe that these cases are undoubtedly of bacterial origin, but that a variety of organisms may be responsible for the mischief. My observations serve to confirm this belief.

Nevertheless, even with a chain of evidence as complete as furnished in my Case 1, the possibility must not be overlooked that we may have been dealing throughout with organisms which invaded the joints only after the working of some other process had rendered them liable to infection. There can be no doubt that this may occur. In Case 2 the traumatic factor seems to have determined the unusual localization in a single joint; it is conceivable that in the absence of this factor the organism found there would have come to an untimely end without producing any more effects than in the healthy rabbit into which it was inoculated.

But the evident infectious character of the onset and of the whole clinical picture in these cases is suggestive. In the same way that predisposition toward all disease in general is determined, the local infectious process appears to be secondary to some factor which lowers the general or local resistance, rather than to any other preceding involvement of the joint—in other words, the joint disturbances are doubtless, *ab initio*, simple infections, but like all conditions of this nature, are much more frequent in individuals whose general condition is below par. As to the constitutional disturbances that frequently mark the onset, we may conceive of them in two ways—as manifestations of a general infection that soon becomes localized in the joints, or, as seems less likely, as caused by secondary general intoxication or actual infection succeeding an initial joint infection.

As to the probable *portals of entry* of such organisms, the same considerations apply here as in the case of a great variety of ordinarily saprophytic or weakly pathogenic organisms, which, under favorable circumstances, are capable of provoking local or even general disturbance. It is not within the province of this report to deal with this phase of the subject. I would merely refer, in passing, to the important work of Adami[16] in this direction, and its abundant confirmation by subsequent observers. A recent communication by Wrzosek[17] promises to shed new light on this matter.

Acute Articular Rheumatism.

Case 4. In this case the same organism was isolated in pure culture from each knee by aspiration. It was artificially cultivated and reproduced satisfactory lesions, clinically and pathologically, in the animal joint into which it was inoculated. It was several times isolated from the latter in pure culture, but could not be demonstrated in the lesions.

With regard to the causal relationship of this organism to the local joint disturbances, the same conclusions apply as in Case 3. The actual heart lesions in acute articular rheumatism, apart from the joints, are too various to consider here.

Relationship of Acute Articular Rheumatism with Infectious Polyarthritis Chronica Villosa.

To the great number of observations recorded in the bacteriological study of acute articular rheumatism I can only refer in general. The results are more at variance than in the less investigated field of infectious polyarthritis chronica villosa. The sum total of evidence, however, is in favor of a varied bacterial origin. Even the emphatic claims of recent English observers to have found a specific cause in the so-called "micrococcus rheumaticus" have been well answered.[9]

Clinically and pathologically, as I have been at pains to point out, the class of cases described by Schüller are distinct from acute articular rheumatism.

Commonly coming under observation only after the chronic condition has developed, their infectious nature is often not recognized, nor is the futility of commonly applied methods of treatment—(dietary, hydrotherapeutic, massage, etc.)—appreciated. The frequent indications for operative interference* explain the interest of these cases to the orthopedic surgeon.

Bacteriologically, however, there is no evidence to show that there is any essential difference between acute articular rheumatism and infectious polyarthritis chronica villosa. The difference in the subsequent course of the two conditions is apparently due to differences in the infecting organisms and in the degree of disturbance they are capable of provoking.

This conception of a similar though not identical etiological relationship is no indication, as I have said, that the two types should not be sharply separated clinically. That this differentiation cannot always be complete must be very evident; points of resemblance occur when, in the chronic type, the general disturbance is considerable and the heart is affected, as in Case 1.

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* It is to be noted that in resorting to surgical measures care must be taken to exclude *atrophic arthritis*, as such treatment is to be applied to this type only in selected cases.

The necessity of a similar bacteriological study of a large number of cases is clear.

It is surprising that with the great interest in bacteriological research in this country, we should have failed to recognize the significance of Schüller's and of Bannatyne's work, and that we have contributed so little to the investigation of this large and important group of cases. No satisfactory work has been done in the bacteriological examination of blood in these cases. This should be a field of special interest, for it is to be pointed out that practically all the results reported in bacteriological study of acute articular rheumatism proceeded from the investigation of materials[*] other than the joint fluid.

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[*] From a fairly complete list of the most important bacteriological work in acute articular rheumatism I have made out a table showing the character of the findings. Out of the positive results of 91 examinations from different materials, 18 were from the blood, 9 from joint fluid, and the rest from various other sources (autopsy materials, excised tonsils, urine, etc.). This does not show the proportion of cases in which the joint fluid was examined without results; there it would appear very much smaller.